The Oxidation of Organic Nitrogen Compounds with Lead Tetra-acetate

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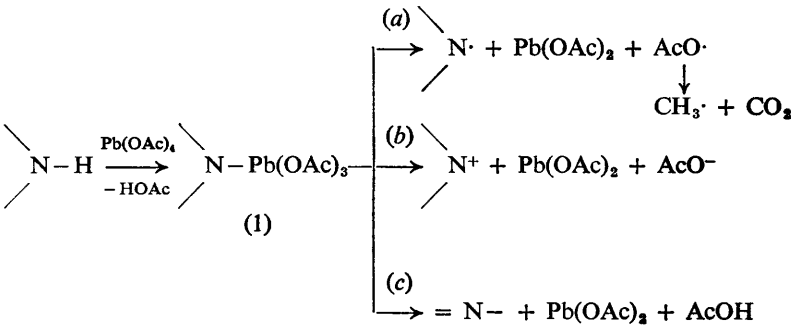
1 Introduction

Lead tetra-acetate (LTA) has been used as an oxidant in organic chemistry for almost fifty years. It is a very versatile reagent and reviews of its reactions with 1,2-glycols,[1] sugars,[2] sterols,[3] and hydrazones,[4] as well as some general reviews,[5] have been published. The general field of organic nitrogen chemistry has not, however, been reviewed.

The emphasis in this report is on reactions and syntheses which are considered under functional group headings. Because of the lack of data only a moderate amount of information on mechanism is included and discussions are limited to reactions where an experimental basis exists in support of a mechanism.

Some introductory remarks on mechanism are necessary. Intermediates of type (1) have been proposed for many of the reactions of LTA with organic nitrogen compounds. These may be formed either by nucleophilic displacement of an acetate ligand or, more likely, by the attack of a lead triacetate cation [from the equilibrium $Pb(OAc)_4 \rightleftharpoons {}^{+}Pb(OAc)_3 + AcO^{-}$] on the nitrogen.



Scheme 1

[1] R. Criegee in C. A. Bunton, 'Oxidation in Organic Chemistry', ed. K. B. Wiberg, Academic Press Inc., New York, 1965, p. 398.
[2] R. S. Perlin, *Adv. Carbohydrate Chem.*, 1959, **14**, 9.
[3] K. Heusler and J. Kalvoda, *Angew. Chem. Internat. Edn.*, 1964, **3**, 525.
[4] R. N. Butler, *Chem. and Ind.*, 1968, 437.
[5] (*a*) R. Criegee, *Angew. Chem.*, 1940, **53**, 321; (*b*) *idem.*, ref. 1, page 278; (*c*) L. F. Fieser and M. Fieser, 'Reagents for Organic Chemistry,' John Wiley Inc., New York, 1967, p. 537.

The decomposition of compound (1) to yield the products or reactive intermediates can be heterolytic or homolytic and in many cases no distinction has been made between either mechanism. Three pathways by which compound (1) may decompose are indicated. In path (*a*) compound (1) decomposes to a nitrogen radical and a lead triacetate radical. The latter should give lead diacetate and the unstable acetoxy radical. In path (*b*) the lead triacetate may be lost as the anion or the loss of acetate ion and lead diacetate and the formation of the nitrogen cation may be concerted. Path (*c*) involves the loss of a proton or cationic group from an atom bonded to the nitrogen. Again lead triacetate may be lost as the anion or in an overall concerted process. A number of other pathways exist for the decomposition of compound (1). Unfortunately, in only a few cases has a systematic study of the reaction conditions, *e.g.* solvent, presence of oxygen, temperature, *etc.* (factors which undoubtedly influence the reaction mechanism), been made and even then a definite mechanism could not always be assigned. Also, compounds of type (1) have not been isolated and the rôle, if any, of co-ordination compounds, *e.g.* the isolable pyridine–LTA complex,[6] has been little explored.

2 Amines

The products from the oxidation (by LTA) of compounds containing the $-NH_2$ group are determined largely by whether it is attached to an alkyl or aromatic residue. Primary alkyl amines are oxidised to the corresponding cyanides in yields of up to 60%.[7] An aldimine (2) formed by the decomposition of an amino-lead triacetate complex in turn forms an imino-lead triacetate complex which decomposes to the cyanide. It has been proposed that in non-polar solvents the decomposition of the lead triacetate intermediates occurs homolytically.[7]

$$RCH_2{\cdot}NH_2 \xrightarrow{Pb(OAc)_4} RCH_2{\cdot}NH{\cdot}Pb(OAc)_3 \xrightarrow[-HOAc]{-Pb(OAc)_2} RC{=}NH \xrightarrow{Pb(OAc)_4} RC{\equiv}N$$

(2)

Scheme 2

Aldimines are also intermediates in the oxidation of aliphatic 1,2-diamines to cyanides,[8] α-amino acids to cyanides and carbon dioxide,[8] 1,2-hydroxyamines to cyanides and aldehydes,[8] and aldehyde–ammonia solutions to cyanides.[9] Cyanides are obtained in very good yields (60—90%) from araldehyde–ammonia solutions.[9]

Triarylmethyl- and 1,1-diphenylethyl-amines are oxidised, with rearrangement, to ketimines.[10] The mechanism of this reaction is uncertain.

[6] R. Partch and J. Monthony, *Tetrahedron Letters*, 1967, 4427.
[7] M. Lj. Mihailovic, A. Stojiljkovic, and V. Andrejevic, *Tetrahedron*, 1967, **23**, 721.
[8] H. J. Roth and A. Brandau, *Arch. Pharm.*, 1960, **293**, 27.
[9] K. N. Parameswaran and O. M. Friedman, *Chem. and Ind.*, 1965, 988; H. J. T. Bos, *Chem. Weekblad*, 1966, **62**, 447.
[10] A. J. Sisti, *Chem. Comm.*, 1968, 1272.

$$Ph_2C(R)\cdot NH_2 \xrightarrow[-HOAc]{Pb(OAc)_4} Ph_2C(R)\cdot NH\cdot Pb(OAc)_3 \xrightarrow[-HOAc]{-Pb(OAc)_2} Ph\cdot C(R) = N\cdot Ph$$

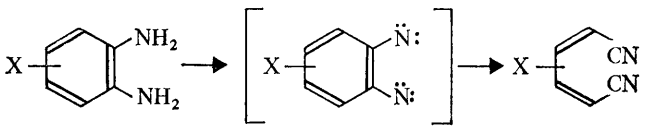
Scheme 3

Azo-compounds are formed, in widely varying yields, from the oxidation of primary aromatic amines.[11–13] Hydrazo-compounds, which are readily oxidised to azo-compounds,[11] are likely intermediates in this reaction. These may be formed by the dimerisation of anilino-radicals (ArNH·)—species which have been observed in the oxidation of 2,4,6-triphenylaniline by LTA.[12] Alternate pathways to the hydrazo-compounds have been suggested.[5b]

$$2ArNH_2 \xrightarrow{Pb(OAc)_4} ArNHNHAr \xrightarrow{Pb(OAc)_4} ArN{=}NAr$$

The side products from this reaction generally include quinone and in some instances this is the major product. Thus, 2-naphthylamine gives 1-(2-naphthalimino)2-acetamido-4-naphthoquinone (60%) and 2-amino-1,4-naphthoquinone (25%). In contrast, the oxidation of 2,4,6-tri-t-butylaniline with LTA yields predominantly 4-acetoxy-1-imino-2,4,6-tri-t-butyl-2,5-cyclohexadiene.[14]

The oxidation of *o*-phenylenediamines is a useful synthetic procedure for the synthesis of *cis*-muconitriles (35—50% yields). A dinitrene has been suggested as an intermediate.[15]



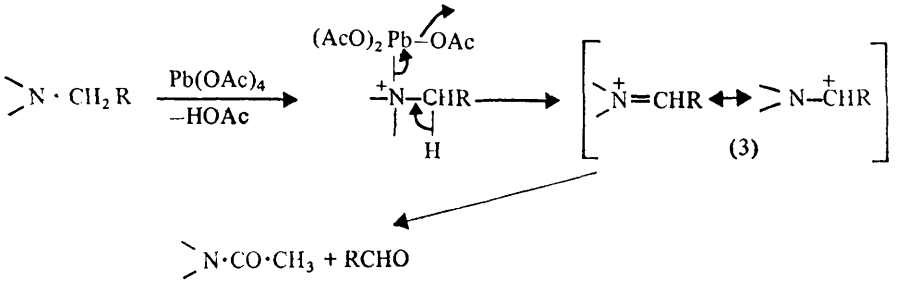
Scheme 4

Secondary amines have received little attention. With one equivalent of LTA dibenzylamine gives benzylidenebenzylamine, benzaldehyde, and benzylamine, as the major products. With two equivalents the main products are benzaldehyde and benzonitrile.[7] Unidentified nitrogen radicals have been observed in the oxidation of diphenylamine.[16]

The reaction conditions and the nature of the substituents on the nitrogen affect the oxidation of tertiary amines appreciably. Under nitrogen *NN*-dialkyl-

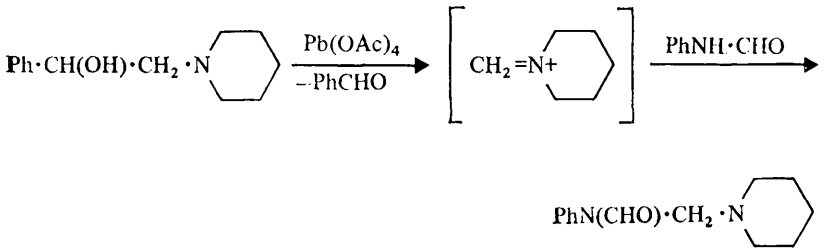
[11] K. H. Pausacker and J. G. Scroggie, *J. Chem. Soc.*, 1954, 4003.
[12] K. Dimroth, F. Falk, and G. Nebauer, *Ber.*, 1957, **90**, 2058.
[13] E. Baer and A. L. Tosini, *J. Amer. Chem. Soc.*, 1956, **78**, 2857; H. J. Richter and R. L. Dressler, *J. Org. Chem.*, 1962, **27**, 4066; H. A. B. Linke, R. Bartha, and D. Pramer, *Z. Naturforsch.*, 1969, **24B**, 994.
[14] R. Okazaki, T. Hosogai, M. Hashimoto, and N. Inamoto, *Bull. Chem. Soc. Japan*, 1969, **42**, 3559.
[15] K. Nakagawa and H. Onoue, *Chem. Comm.*, 1965, 396.
[16] H. Lemaire and A. Rassat, *Tetrahedron Letters*, 1964, 2245.

anilines are cleaved by LTA in chloroform–acetic anhydride to give aldehyde (50—93%) and *N*-acetyl-*N*-alkylaniline (20—90%).[17] A immonium ion of type (3) is a probable intermediate in this reaction.



Scheme 5

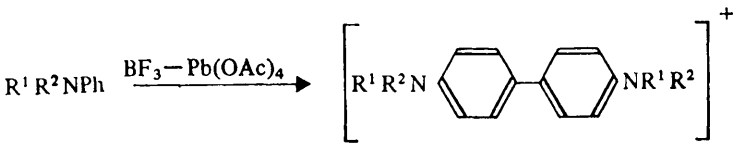
Similar immonium ions have been suggested as intermediates in the oxidation of 1,2-dihydroxy tertiary amines to the appropriate carbonyl compounds and secondary amines.[18,19] In the case of 1-phenyl-2-piperidinoethanol the intermediate charged species, the methylene piperidinium ion, has been trapped using formaldehyde–aniline.[20]



Scheme 6

With LTA–BF_3, *NN*-dimethylaniline behaves differently and the *NNN'N'*-tetramethylbenzidine radical cation is formed. Triphenylamine gives the radical cation both in the presence of, and absence of, boron trifluoride.[21] The rôle of the boron trifluoride in these reactions is unclear and the mechanism for the formation of the radical cation has not been established.

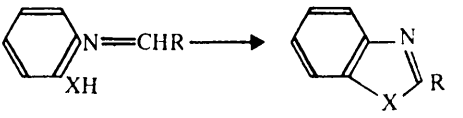
[17] L. Horner, E. Winkelmann, K. H. Knapp, and W. Ludwig, *Ber.*, 1959, **92**, 288.
[18] N. J. Leonard and M. Rebenstorf, *J. Amer. Chem. Soc.*, 1945, **67**, 49.
[19] H. J. Roth, *Arch. Pharm.*, 1961, **294**, 427.
[20] H. Mohrle and P. Spillman, *Tetrahedron*, 1965, **25**, 5598.
[21] D. L. Allara, B. C. Gilbert, and R. O. C. Norman, *Chem. Comm.*, 1965, 319.



Scheme 7

N-Substituted carbazoles give the 3,3′-dicarbazole cation radical with LTA–BF_3 or LTA–$HClO_4$ while tri-*p*-tolylamine gives a quantitative yield of the tri-*p*-tolylnitrogen radical under the same conditions.[22]

Benziminazoles and benzoxazoles have been synthesised in good yields from the appropriately substituted Schiff's bases, the yields of benziminazoles being superior to those obtained from the Skraup synthesis.[23]



[X = NH, O]

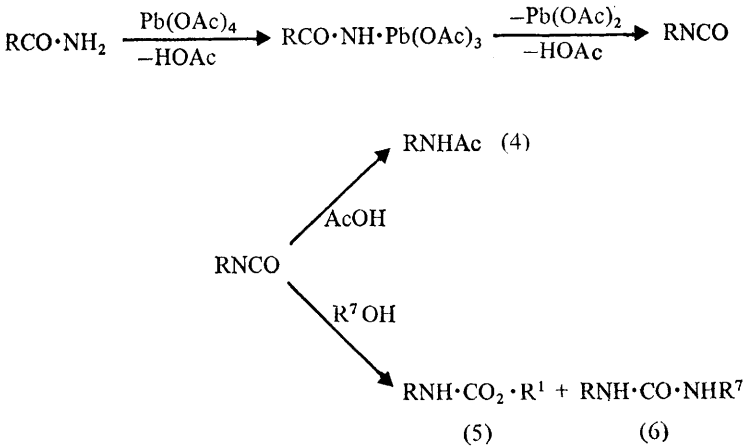
Scheme 8

3 Amides

The oxidation of primary amides with LTA parallels the Hofmann reaction and is in some cases a superior synthetic pathway.[24–26] Generally, the products isolated are those resulting from further reaction of the initially formed isocyanate. The isocyanates can be isolated when the reaction is carried out in non-polar solvents.[24] In acetic acid an acylamine (4) is the major product[25] while in alcohol good yields (33—96%) of *N*-substituted carbamates (5) and small amounts of *NN*-disubstituted ureas (6) are obtained.[26]

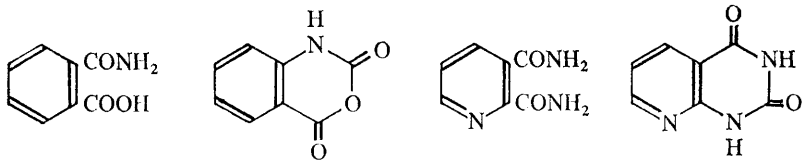
This reaction is characterised by high selectivity when applied to compounds containing other functional groups. Apparently the isocyanate is formed *via* a concerted rearrangement of the lead–amide complex as no free nitrenes have been observed.[26] When the molecule contains a suitably situated carbonyl or carbamyl group intramolecular cyclisation with the isocyanate group can occur, giving 6-membered heterocyclic rings. Thus, phthalaminic acid (7) gives isatoic

[22] D. H. Illes and A. Ledwith, *Chem. Comm.*, 1968, 498.
[23] F. F. Stephen and J. D. Bower, *J. Chem. Soc.*, 1949, 2971; 1950, 1772.
[24] H. E. Baumgarten and A. Staklis, *J. Amer. Chem. Soc.*, 1965, **87**, 1141.
[25] B. Acott and A. L. J. Beckwith, *Chem. Comm.*, 1965, 161.
[26] B. Acott, A. L. J. Beckwith, A. Hassanali, and J. Redmond, *Tetrahedron Letters*, 1965, **45**, 4039; B. Acott, A. L. J. Beckwith, and A. Hassanali, *Austral. J. Chem.*, 1968, **21**, 185, 197.



Scheme 9

anhydride (8) while pyridine 2,3-dicarboxamide (9) gives a pyrido-pyrimidine derivative (10).[27]



(7) (8) (9) (10)

This is a general synthetic method and a number of similar cyclisations have been accomplished with yields superior, in many cases, to those obtained from the Hofmann reaction.[26,27]

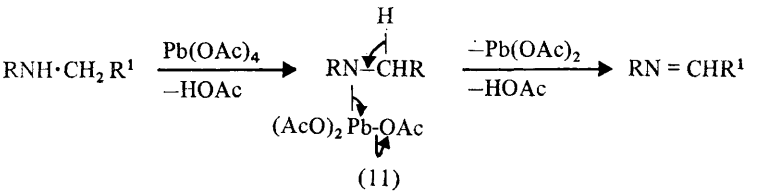
In the presence of iodine LTA reacts with primary amides to give *N*-iodoamides. The photolysis of steroidal *N*-iodoamides so formed is a useful synthesis of steroidal lactones.[28]

Carbamates and imides do not react with LTA.[26,29]

The reactions of *N*-substituted amides depend largely on the nature of the *N*-substituent. In general, *N*-alkyl acetamides and benzamides are unreactive[8,30]

[27] A. L. J. Beckwith and R. Hickman, *Austral. J. Chem.*, 1968, **21**, 2756.
[28] D. H. R. Barton and A. L. J. Beckwith, *Chem. Comm.*, 1963, 335.
[29] R. M. Moriarty, H. G. Walsh, and H. Gopal, *Tetrahedron Letters*, 1966, 4363.
[30] F. Knopp, F. Ditt, W. Hecksteden, J. Maier, W. Mertz, and R. Harle, *Z. physiol. Chem.*, 1936, **239**, 30.

while *N*-alkyl sulphonamides[8] and *N*-alkyl ethoxycarbonyl derivatives are dehydrogenated to imines[31] *via* the *N*-lead triacetate intermediate (11).

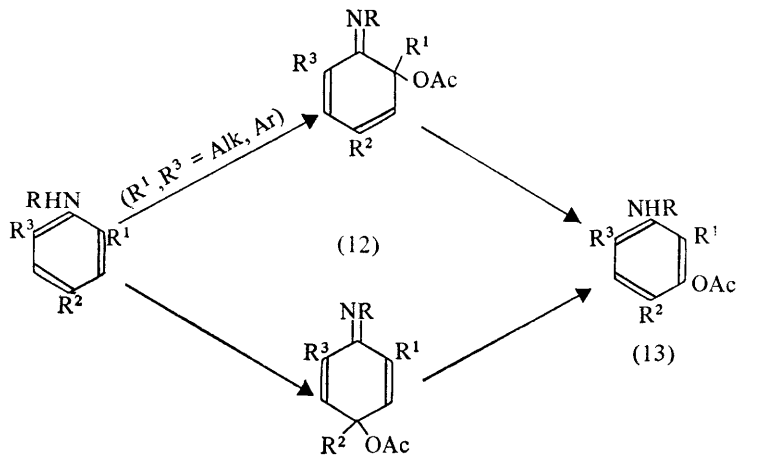


(11)

[R = CO_2 Et, Tosyl]

Scheme 10

N-Aryl amides are readily oxidised in chloroform solutions to give products which vary with the substitution pattern in the aromatic ring. Benzoquinolimide acetates (12) or, more generally, the rearranged acetates (13) are the major products.[32]

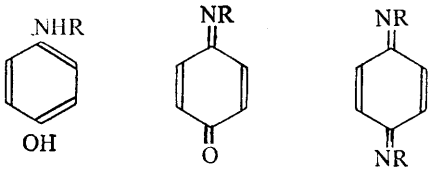


[R = Ac, ArCO, $ArSO_2$]

Scheme 11

[31] P. Karrer and J. Meyer, *Helv. Chim. Acta*, 1937, **20**, 407.
[32] R. Adams, E. Angello, and R. S. Colgrove, *J. Amer. Chem. Soc.*, 1955, **77**, 5617; R. Adams and L. M. Werkel, *ibid.*, 1955, **80**, 5799.

Phenolic derivatives (14) readily give quinone monoimides (15)[33–35] while quinone di-imides, *e.g.* compound (16), are formed from the diamides of *o*- and *p*-phenylenediamines.[33,35]

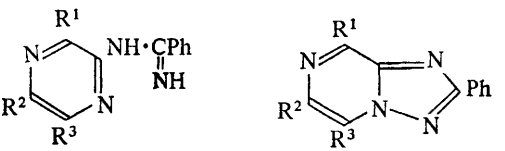


(14) (15) (16)

The mono and di-imides are useful synthetic intermediates, adding a variety of substances, *e.g.* hydrogen cyanide, hydrazoic acid, alcohols, water, *etc.*, to give substituted aromatic compounds. The scope of these reactions has been reviewed.[35,36]

Naphthalene derivatives behave somewhat differently: 1-benzamidonaphthalene gives 4-benzamido-1-naphthol acetate (60%), while 2-benzenesulphonamidonaphthalene gives predominantly 1,4-naphthoquinone.[34] Acenaphthene derivatives generally give quinolimide acetates[37] although exceptions are known.[38]

The oxidation of suitably substituted amidines has been used to prepare cyclic derivatives. Thus, *N*-2-pyrazinylbenzamidines (17) give 2-phenyl-*s*-triazolo-[2,3-*a*]pyrazine derivatives (18).[39]



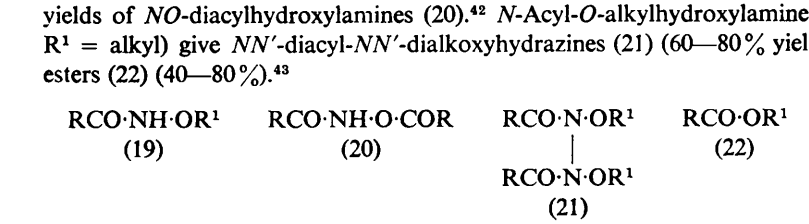
(17) (18)

[33] R. Adams and J. L. Anderson, *J. Amer. Chem. Soc.*, 1950, **72**, 5154; R. Adams and J. W. Way, *ibid.*, 1954, **76**, 2763.
[34] H. J. Richter and R. L. Dressler, *J. Org. Chem.*, 1962, **27**, 4066.
[35] R. Adams and A. Nagarkatti, *J. Amer. Chem. Soc.*, 1950, **72**, 4601; J. L. Soto, *Anales Real. Soc. Espan. Fis. Quim. (Madrid)*, 1967, **63-B**, 889; 1969, **65-B**, 583.
[36] R. Adams and W. Reifschneider, *Bull. Soc. chim. France*, 1958, 23.
[37] H. J. Richter and W. C. Feist, *J. Org. Chem.*, 1961, **26**, 3133.
[38] H. J. Richter, R. L. Dressler, and S. F. Silver, *J. Org. Chem.*, 1965, **30**, 4078.
[39] G. M. Badger, P. J. Nelson, and K. T. Potts, *J. Org. Chem.*, 1964, **29**, 2542.

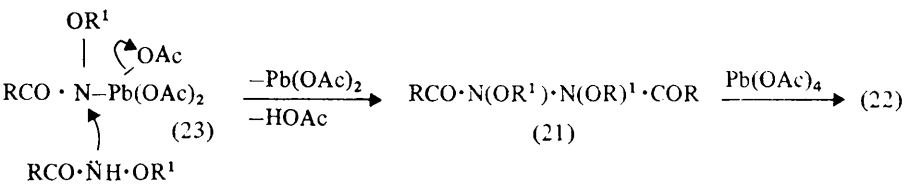
Similar cyclisations have been accomplished with *N*-3-pyrazinylacetamidines[40] and *N*-2-pyridylamidines.[41]

4 Hydroxylamine Derivatives

The oxidation of *N*-acylhydroxylamines (19; R^1 = H) with LTA gives good yields of *NO*-diacylhydroxylamines (20).[42] *N*-Acyl-*O*-alkylhydroxylamines (19; R^1 = alkyl) give *NN'*-diacyl-*NN'*-dialkoxyhydrazines (21) (60—80% yields) or esters (22) (40—80%).[43]

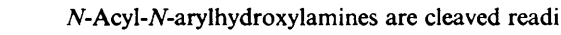


The hydrazine (21) is formed by attack of unreacted hydroxylamine on the hydroxylamine–lead triacetate complex (23). The hydrazine is stable only when R = R^1 = alkyl, otherwise it undergoes further oxidation to an unstable azo-compound which decomposes with loss of nitrogen to give the ester (22).[43]



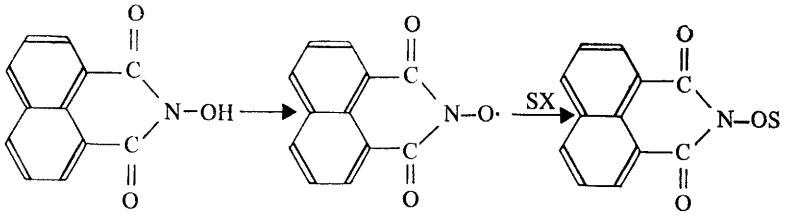
Scheme 12

N-Acyl-*N*-arylhydroxylamines are cleaved readily at low temperatures to give arylnitroso-compounds (40—80%).[44] An ionic mechanism has been proposed for this reaction.[44]



In contrast, the oxidations of *N*-hydroxynaphthalimide and *N*-hydroxy-phthalimide give products derived mainly from the reaction of the nitroxide radical, which has been observed spectroscopically, with the solvent.[45]

[40] T. Okamoto, Y. Torigoe, M. Sato, and Y. Isogai, *Chem. and Pharm. Bull. (Japan)*, 1968, **16**, 1154.
[41] J. D. Bower and G. Ramage, *J. Chem. Soc.*, 1957, 4506.
[42] J. E. Rowe and A. D. Ward, *Austral. J. Chem.*, 1968, **21**, 2761.
[43] J. A. Cooley, M. W. Mosher, and M. A. Khan, *J. Amer. Chem. Soc.*, 1968, **90**, 1867.
[44] H. E. Baumgarten, A. Staklis, and E. M. Miller, *J. Org. Chem.*, 1965, **30**, 1203.
[45] A. Calder, A. R. Forrester, and R. H. Thomson, *J. Chem. Soc.* (*C*), 1969, 512.



[S = Ph, $PhCH_2$, CCl_3; X = H, Cl]

Scheme 13

The oxidation of oximes with LTA has received considerable attention because of the readiness with which it gives iminoxy-radicals.[46,47]

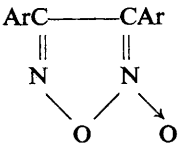
$$R^1R^2C{=}N{\cdot}OH \xrightarrow{LTA} R^1R^2C{=}NO{\cdot}$$

The iminoxy-radicals are σ-radicals, some of which are stable at room temperature while others require the use of flow techniques.[48] Generally, both the *syn*- and *anti*-isomers are formed irrespective of the configuration of the starting oxime, indicating that the configurational stability of the C–N bond is not as great in the radical as in the oxime. These radicals exhibit both long range interactions as well as interactions across space.[48] The pattern of halogen splitting has been studied[49] and the conformational preferences of the radicals can be deduced from structure–spin correlations.[50]

The products isolated from the oxidation of oximes arise, however, from both ionic and free radical processes. They vary also with the nature of the substrate, the solvent, the ratio of oxidant to substrate, and the presence of nitric oxide.[51] The oxidation of aliphatic aldoximes (24; R = alkyl) in ether at −30 °C gives *trans*-bis(nitrosoacetoxyalkanes) (25) (40—70% yields),[52] while aromatic aldoximes (24; R = aryl) at 0 °C give aldoxime anhydride *N*-oxides (26) (19—51% yields).[53] The cyclisation of benzil and phenanthrene dioximes to furoxan derivatives (27) is a similar reaction.[52]

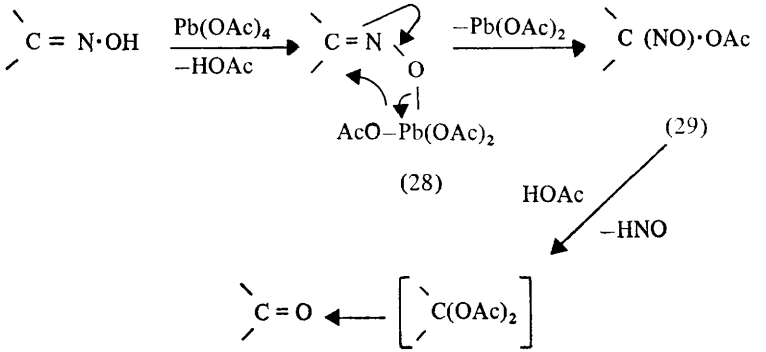
[46] M. Bethoux, H. Lemaire, and A. Rassat, *Bull. Soc. chim. France*, 1964, 1985.
[47] J. W. Lown, *J. Chem. Soc.* (*B*), 1966, 441; 1966, 644.
[48] B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc.* (*B*), 1966, 86; 1966, 722; *J. Phys. Chem.*, 1967, **71**, 14.
[49] B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc.* (*B*), 1967, 981.
[50] B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc.* (*B*), 1968, 123; B. C. Gilbert and M. Gulick, *J. Phys. Chem.*, 1969, **73**, 2448.
[51] M. M. Frojmovic and G. Just, *Canad. J. Chem.*, 1968, **46**, 3719.
[52] H. Kropf and R. Lambeck, *Annalen*, 1966, **700**, 1.
[53] H. Kropf and R. Lambeck, *Annalen*, 1966, **700**, 18.

$RCH{=}N{\cdot}OH$ (24) $RCH(OAc){\cdot}N(O){=}N(O){\cdot}CH(OAc)R$ (25) $RCH{=}N(O){\cdot}O{\cdot}N{=}CHR$ (26)



(27)

In inert solvents and at low temperatures aliphatic alicyclic ketoximes give 1,1-nitrosoacetoxyalkanes (29) (10—75% yields)[52–55] *via* the intramolecular decomposition of the lead triacetate complex (28).[52] In acetic acid both aromatic and aliphatic ketoximes give the parent carbonyl compounds.[56] It appears that the carbonyl compounds arise from the decomposition of the nitrosoacetate in acetic acid.[52]

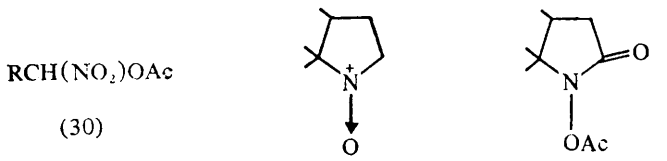


Scheme 14

A number of arylketoximes have been reported to give ketones, azine monoxides, and 1,1-dinitro-compounds *via* a free radical type mechanism[57] while sterically hindered aldoximes and ketoximes are oxidised to hydroxamic acid derivatives, *e.g. syn*-trimethylacetaldoxime gives *N*-acetoxytrimethylacetohydroxamic acid.[58]

[54] D. C. Iffland and D. X. Criner, *Chem. and Ind.*, 1956, 176.
[55] S. Kaufman, L. Tokes, J. W. Murphy, and P. Crabbe, *J. Org. Chem.*, 1969, **34**, 1618.
[56] Y. Yukawa, M. Sakai, and S. Suzuki, *Bull. Chem. Soc. Japan*, 1966, **39**, 2266.
[57] G. Just and K. Dahl, *Tetrahedron*, 1968, **24**, 5251; *Canad. J. Chem.*, 1970, **48**, 966.
[58] J. J. Riehl and Fr. Lamy, *Chem. Comm.*, 1969, 406.

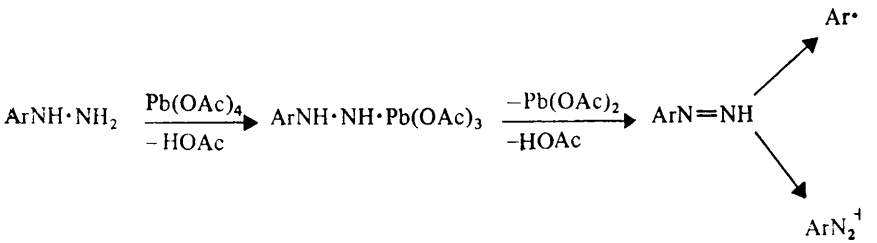
Nitroalkanes[59] and some *N*-oxides[60,61] react somewhat similarly to oximes. Thus, 1-acetoxy-1-nitroalkanes (30) are formed from nitroalkanes,[59] while 4,5,5-trimethyl-1-pyrroline-1-oxide (31) gives the *N*-acetoxypyrrolidine-2-one derivative (32) (64% yield).[60]



(30) (31) (32)

5 Hydrazines

Arylhydrazines are oxidised, *via* aryldi-imides, to aryl diazonium ions at low temperatures, and to aryl radicals at ambient temperatures.[61]

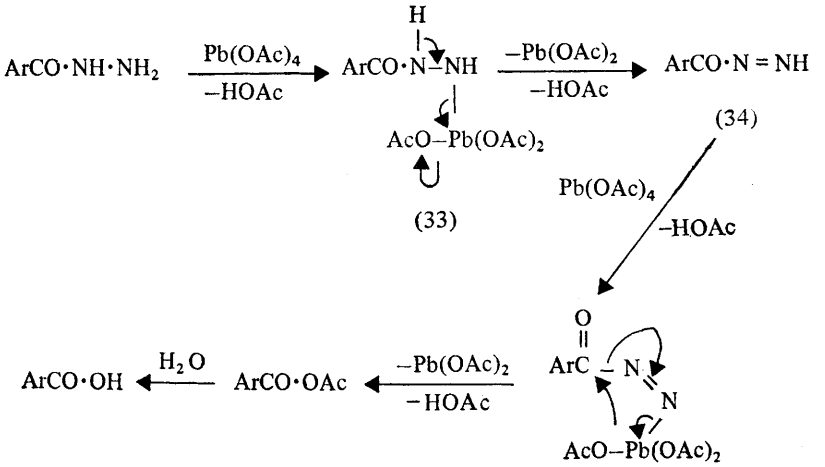


Scheme 15

When monoaroylhydrazines are added to two equivalents of LTA the corresponding aroic acids are isolated in excellent yields. Aroyl di-imides (34) are intermediates. Further reaction of the aroyl di-imide–lead triacetate complex (35) seems to occur *via* an intramolecular mechanism.[62]

When the mode of addition is reversed *NN'*-diacylhydrazines, formed *via* attack of unreacted hydrazide on the carbonyl group of the aroylhydrazine–lead triacetate complex (33), are the main products.[62]

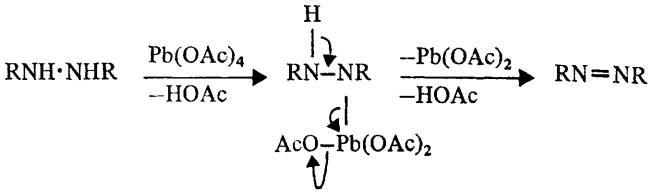
[59] L. A. Neiman, S. I. Kirillova, V. A. Maimind, and M. M. Shemyakin, *Zhur. obshchei. Khim.*, 1965, **35**, 1932 (*Chem. Abs.*, 1966, **64**, 6534*f*).
[60] N. J. Gutteridge and F. J. McGillan, *J. Chem. Soc.*, 1970. 641; A. Otha, *Chem. and Pharm. Bull. Japan*, 1963, **11**, 1586.
[61] J. B. Aylward, *J. Chem. Soc.* (*C*), 1969, 1633.
[62] J. B. Aylward and R. O. C. Norman, *J. Chem. Soc.* (*C*), 1968, 2399.



Scheme 16

LTA has been used in the oxidation of a large variety of *NN'*-disubstituted hydrazines to azo-compounds (Scheme 17).[63–70]

Many of the azo-compounds formed can be isolated but some, especially the *NN'*-dicarbonylazo-compounds and their cyclic analogues, are thermally unstable.[65] These materials, which are very reactive dieneophiles,[66] are generated



Scheme 17

[63] S. G. Cohen and J. Nicholson, *J. Amer. Chem. Soc.*, 1965, **30**, 1165; R. W. Hoffmann, *Ber.*, 1964, **97**, 2763, 2772; 1965, **98**, 222; R. W. Hoffmann and K. R. Eicken, *Ber.*, 1967, **100**, 1465; S. Hunig and G. Kraup, *Annalen*, 1966, **700**, 65; P. C. Huang and E. M. Kosower, *J. Amer. Chem. Soc.*, 1968, **90**, 2354; H. Milne and C. F. Frost, *J. Org. Chem.*, 1968, **33**, 169.

[64] R. A. Clement, *J. Org. Chem.*, 1960, **25**, 1724; 1962, **27**, 1115.

[65] E. Fahr and H. Lind, *Angew. Chem. Internat. Edn.*, 1966, **5**, 372.

[66] J. Sauer and B. Schroeder, *Ber.*, 1967, **100**, 678.

[67] B. T. Gillis and R. Weinkam, *J. Org. Chem.*, 1967, **32**, 3321.

[68] R. H. Kent and J. P. Anseline, *Canad. J. Chem.*, 1968, **46**, 2322; M. Rosenblum, A. Longroy, M. Neveu, and C. Steel, *J. Amer. Chem. Soc.*, 1965, **87**, 5716.

[69] W. Nagata and S. Kamata, *J. Chem. Soc.* (*C*), 1970, 540.

[70] C. W. Rees and M. Yelland, *Chem. Comm.*, 1969, 377.

in situ in the presence of a diene. In the absence of the diene they decompose, *e.g.* phthalhydrazide gives phthalic acid and a polymer.[67] Monocarbonylazo-compounds are less reactive and thermally more stable, and may be isolated. However, cyclic derivatives with a carbonyl group adjacent to the azo-function are unstable and decompose to give an olefin, nitrogen, and carbon monoxide[67,68] *e.g.* 3,4-diphenylpyrazolindin-5-one gives *trans*-stilbene, nitrogen, and carbon monoxide.[67] Some of the monocarbonylazo-compounds can, however, be isolated, *e.g.* pyrazoline-3-one derivatives[69] and some have been trapped by dienes.[67,70]

NN-Disubstituted hydrazines are readily oxidised by LTA to give a variety of compounds. The hydrazines have been divided into two categories:[71] those which undergo predominantly intermolecular reactions, and those which undergo predominantly extrusion and intramolecular reactions. The reactive intermediate in the oxidation of the first category of hydrazines with LTA appears to be an *N*-nitrene (amino-nitrene) (36) in the singlet state, stabilised by delocalisation which increases the nucleophilic character of the nitrene.[71]

$$R_2N{\cdot}NH_2 \xrightarrow{Pb(OAc)_4} [R_2N-N: \rightleftharpoons R_2\overset{+}{N}=\overset{-}{N}]$$

(36)

In the absence of a trapping agent intermolecular reaction, *via* the *N*-nitrene, will generally give tetrazenes or products derived from the decomposition of tetrazines. Thus, *NN*-diakyl-, *NN*-diaryl-, and *NN*-diaralkyl-hydrazines are oxidised by LTA at -60 °C to give tetrazenes (37)[72] in high yields, while at room temperature *NN*-dibenzylhydrazine gives benzyl azide and benzaldehyde as the main products.[73] These same products are isolated from the reaction of 1,1,4,4-tetrabenzyltetrazene with LTA.[73] *N*-Aminophthalimide gives 1,4-diphthalyltetrazene and phthalimide.[74] In some cases it is the deaminated compound that is the major product[71]—this may arise from tetrazene decomposition.[74] Aminonitrenes, generated from the first category of hydrazines, have been trapped by olefins,[71,74,75] dienes,[75] and dimethylsulphoxide.[70,75] The reaction with olefins and dienes is a very convenient method of aziridine (38) synthesis.[74–76]

$$R_2N{\cdot}N=N{\cdot}NR_2$$

(37)

(38)

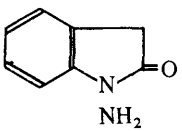
[71] D. J. Anderson, T. L. Gilchrist, D. C. Howell, and C. W. Rees, *J. Chem. Soc.* (*C*), 1970, 576.
[72] R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, 1964, **64**, 149; M. J. Harrison, R. O. C. Norman, and J. B. Aylward, unpublished work.
[73] G. Koga and J. P. Anselme, *J. Amer. Chem. Soc.*, 1969, **91**, 4323.
[74] L. Hoesch and A. S. Dreiding, *Chimia*, 1969, 405.
[75] M. Baudru and A. Foucard, *Compt. rend.*, 1970, **270***C*, 104.
[76] R. S. Atkinson and C. W. Rees, *J. Chem. Soc.* (*C*), 1969, 772.

Addition to *cis*- and *trans*-olefins is stereoselective, indicating that the *N*-nitrene is in the singlet state.[71,75] Also, olefins substituted with electron-withdrawing groups are as successful as the conventional olefinic traps, a factor supporting the nucleophilic nature of this intermediate.[71] An *O*-nitrene (39) has been generated in the oxidation of methoxyamine with LTA and has been trapped as the aziridine derivative (40).[77]

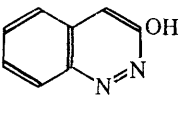
$$MeONH_2 \xrightarrow{Pb(OAc)_4} [MeO\ddot{N}: \rightleftharpoons MeO^{+}=N^{-}] \longrightarrow >C-C<$$

(39) $\qquad\qquad$ N·OMe (40)

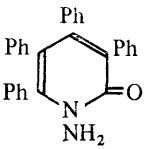
Some *N*-nitrenes, in a suitable environment, are capable of undergoing ring expansion rather than tetrazene formation. Thus, Neber's lactone (41) gives 3-cinnolinol (42).[78] The formation of 3,4,5,6-tetraphenylpyridazine (44) (60%) from 3,4,5,6-tetraphenyl-1-amino-pyridine-2-one (43) also involves an insertion but this is accompanied by the extrusion of carbon monoxide.[70]



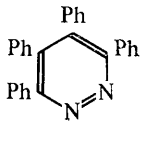
(41)



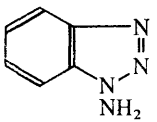
(42)



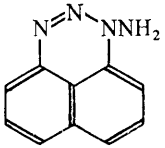
(43)



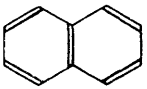
(44)



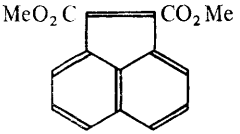
(45)



(46)



(47)



(48)

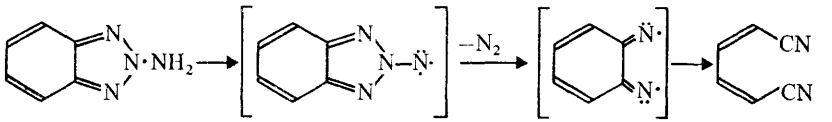
When the *NN*-disubstituted hydrazine is part of a triazole ring, nitrogen is lost. 1-Aminotriazoles readily lose two moles of nitrogen; thus, 1-aminobenzotriazole (45) gives benzyne and biphenylene is isolated in high yields in the absence of a

[77] S. J. Brois, *J. Org. Chem.*, 1970, **92**, 1079.
[78] H. E. Baumgarten, P. L. Creger, and R. L. Zey, *J. Amer. Chem. Soc.*, 1960, **82**, 3977.

trapping agent.[79] Cycloheptyne[80] and a number of arynes[81,82] have been generated from the appropriate 1-aminotriazoles. These '*yne*' intermediates are readily trapped in good yields as their tetracyclone adducts. A similar reaction is the oxidation of 1-aminonaphtho[1,8-*de*]triazine (46) to 1,8-didehydronaphthalene (47) which has been trapped by cyclo-addition to dimethylacetylenedicarboxylate (48).[83,84]

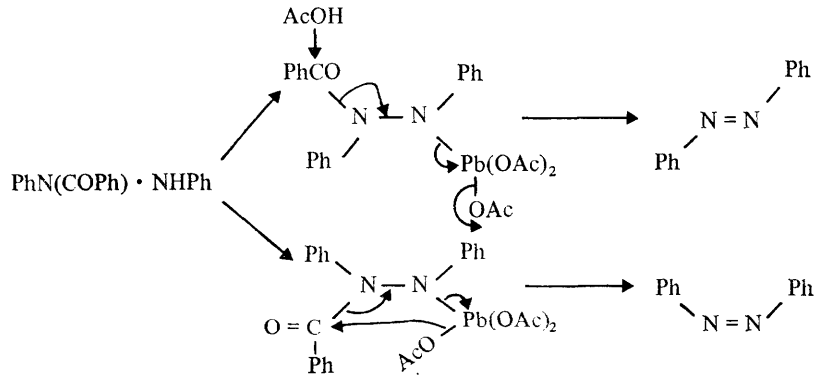
If an intermediate *N*-nitrene is generated in the above reactions it decomposes too rapidly to be trapped.[79]

The oxidation of 2-aminobenzotriazole with LTA occurs with the loss of one mole of nitrogen to give *cis*-muconitriles;[85] this may proceed *via* the *N*-nitrene to a dinitrene to the *cis*-muconitrile (*cf.* the oxidation of *o*-phenylene diamines above).



Scheme 18

N-Benzoyl-*NN'*-diphenylhydrazine gives a mixture of *cis*- and *trans*-azobenzene. The major product, the *trans*-isomer, arises from external nucleophilic

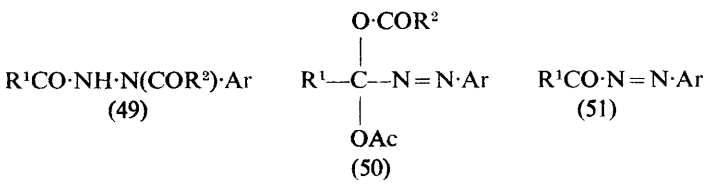


Scheme 19

[79] C. D. Campbell and C. W. Rees, *J. Chem. Soc.* (*C*), 1969, 743.
[80] G. Wittig and J. Meske-Schuller, *Annalen*, 1968, **711**, 65.
[81] C. W. Rees and R. C. Storr, *J. Chem. Soc.* (*C*), 1969, 761; C. W. Rees and D. E. West, *Chem. Comm.*, 1969, 647.
[82] C. W. J. Fleet and I Fleming, *J Chem. Soc.* (*C*), 1969, 1758.
[83] C. W. Rees and R. C. Storr, *Chem. Comm.*, 1965, 193.
[84] R. W. Hoffmann, G. Guhn, M. Preiss, and B. Dittrich, *J. Chem. Soc.* (*C*), 1969, 769.
[85] C. D. Campbell and C. W. Rees, *Chem. Comm.*, 1965, 192.

attack on the carbonyl group while the *cis*-isomer arises from intramolecular acetate transfer.[86]

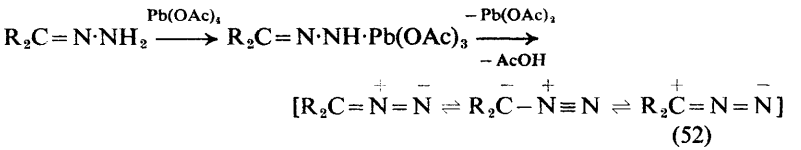
N-Aryl-*NN'*-diacylhydrazines (49) give azodiacylals (50) and azoacylbenzenes (51).[86–88] Protic solvents favour the acylazobenzenes while aprotic solvents favour the azoacylals.[86]



(49) (50) (51)

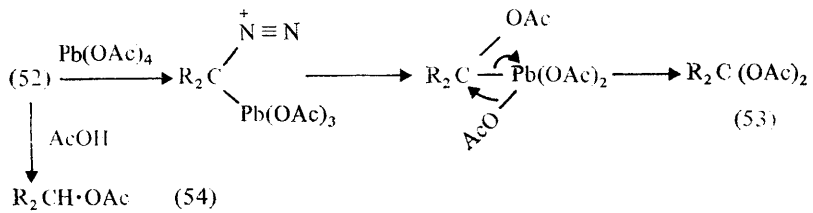
6 Hydrazones and Derivatives

N-Unsubstituted hydrazones are dehydrogenated to the corresponding diazo-compounds (52) *via* a hydrazone–lead triacetate complex.[89]



(52)

Only the more stable bis(trifluoromethyl)-,[90] dicyano-,[91] and diphenyl-[92] diazomethane derivatives have been isolated. Generally, the diazoalkane will react with a further molecule of LTA to give the diacetoxy-derivative (53) or with acetic acid to give the acetoxy-alkane (54).[89]



(53) (54)

Scheme 20

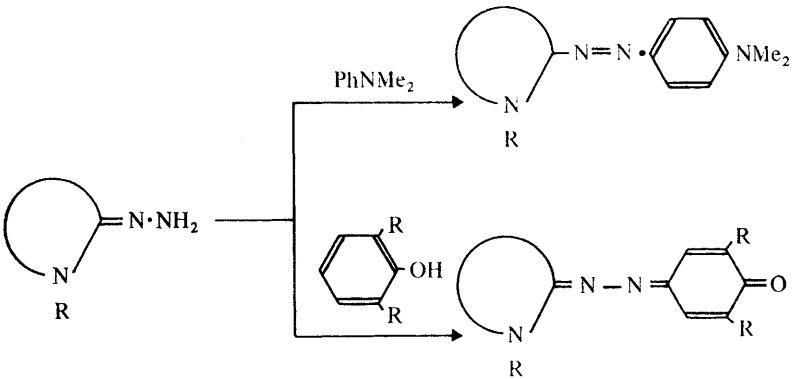
[86] W. A. F. Gladstone, *J. Chem. Soc.* (*C*), 1969, 1571.
[87] W. A. F. Gladstone, *Chem. Comm.*, 1969, 179.
[88] W. A. F. Gladstone, J. B. Aylward, and R. O. C. Norman, *J. Chem. Soc.* (*C*), 1969, 2587.
[89] A. Stojiljkovic, N. Orbovic, S. Sredojevic, and M. Lj. Mihailovic, *Tetrahedron*, 1970, **26**, 1101.
[90] J. Jacques, C. Wiedmann, and A. Horeau, *Bull. Soc. chim. France*, 1959, 424.
[91] D. M. Gales, W. T. Middleton, and C. G. Krespan, *J. Amer. Chem. Soc.*, 1965, **87**, 657.
[92] E. Ciganek, *J. Org. Chem.*, 1965, **30**, 4193.

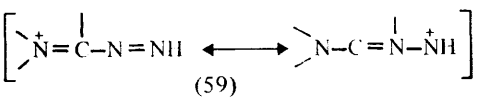
In dichloromethane–acetic acid the monoacetoxy-derivative is the major product while in dichloromethane–pyridine the major product is the diacetoxy derivative.[89] The reaction of diazoalkanes with LTA to give diacetoxyalkanes, and with acetic acid, to give the acetoxy-alkane, supports this mechanism.[89,93] Steroidal hydrazones in methylene dichloride have been oxidised to acetoxy-alkanes, the other major products being alkenes.[94,95] Apparently in these cases proton loss and reaction with acetic acid are competitive. Dicylohexyl formaldehyde hydrazone (55) behaves similarly giving the acetoxy-alkane (56) in 43% yield and the olefins (57) and (58) in 48% and 8% yields respectively.[94]

$(C_6H_{11})_2C{:}N{\cdot}NH_2$ (55) $(C_6H_{11})_2CH{\cdot}OAc$ (56) $C_6H_{11}{\cdot}CH=$ (57)

$C_6H_{11}{\cdot}CH_2{\cdot}$ (58)

The oxidation of hydrazone systems, or particularly those contained in amidrazone systems ($>N-C=NNH_2$) or their vinyl analogues [$>N-(C=C)_n-C=NNH_2$], has been used to introduce azo-groups into aromatic amines, phenols, and activated methylene compounds.[96,97] These reactions are similar to those observed in the oxidative coupling of *p*-phenylenediamines[97] and LTA is only one of the many oxidants used. Some examples are given here.





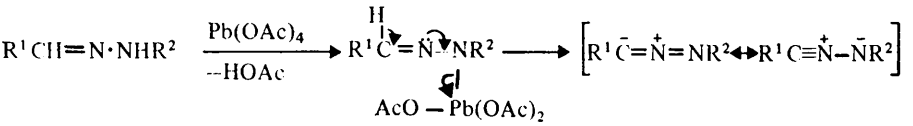
(59)

Scheme 21

[93] H. R. Hensel, *Ber.*, 1955, **88**, 527.
[94] D. H. R. Barton, P. L. Batten, J. F. McGhie, *J. Chem. Soc.* (*C*), 1970, 1033.
[95] M. Debono and R. M. Molloy, *J. Org. Chem.*, 1969, **34**, 1454; A. A. Akhrem, A. V. Kamernitskii, and I. G. Reshetova, *Izvest. Akad. Nauk. S.S.S.R., Ser. Khim.*, 1970, 163.
[96] S. Hunig, W. Brenniger, H. Giger, G. Kaupp, W. Kneise, W. Lampe, H. Quast, R. D. Rauschenbach, and A. Schutz, *Angew. Chem. Internat. Edn.*, 1968, **7**, 335.
[97] S. Hunig, *J. Chem. Educ.*, 1969, **46**, 734.

Apparently the intermediate in these coupling reactions is the species (59). *N*-Sulphonylhydrazones couple by way of the intermediate ($>\overset{+}{N}=\underset{|}{C}-N=NSO_2R$).[97]

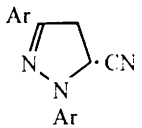
The oxidation of aldehyde *N*-substituted-hydrazones with LTA provides a convenient method for the generation of nitrilimines.[87,88]



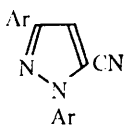
Scheme 22

Aldehyde *N*-alkyl-*N*-substituted hydrazones undergo oxidative cleavage (*cf.* cleavage of tertiary amines above) to give aldehyde and aldehyde hydrazone, which reacts further to the nitrilimine.[98]

Aryl nitrilimines can be trapped as pyrazolines (60) or, more generally, as the further oxidised species 1,3-diarylpyrazole-5-carbonitriles (61) when the reaction is carried out in acrylo-nitrile.[88,98] In methanol hydrazonyl acetates (62) are formed, while in acetic acid or inert solvents the products are *N*-acetyl-derivatives (63). Benzaldehyde phenylhydrazone is an exception in that the azoacetate (64) is formed in inert solvents and acetic acid under anaerobic conditions.[88]



(60)



(61)

$RC(OCH_3){:}N{\cdot}NHR$ (62)

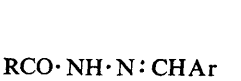
$RCO{\cdot}NH{\cdot}H(COCH_3)R$ (63)

$PhCH(OAc){\cdot}N{:}N{\cdot}Ph$ (64)

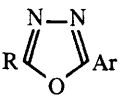
Hydrazones with appropriately located substituents can be oxidised with LTA, *via* the nitrilimine, to heterocyclic materials. Araldehyde acylhydrazones (65; R = Ar) and araldehyde 4,4-diphenylsemicarbazones (65; R = NPh_2) give oxadiazoles (66),[88] *o*-nitrobenzaldehyde arylhydrazones give benzisoxazole-1-oxides (67),[88] while a whole range of *s*-triazolo-derivatives (68) have been prepared from the appropriate aldehyde *N*-heterocyclic-hydrazones.[4,99] High yields of the heterocyclic materials are obtained, although in some cases cyclisation and the formation of the diacylhydrazines (63) are competitive.[4]

[98] J. B. Aylward, *J. Chem. Soc.* (*C*), 1970, 1494.

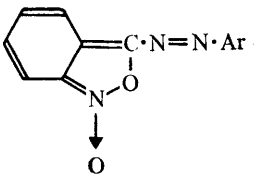
[99] B. Stanovik, M. Tisler, M. Ceglar, and V. Bah, *J. Org. Chem.*, 1970, **35**, 1138; J. Kobe, B. Stanovik, and M. Tisler, *Tetrahedron*, 1970, **26**, 3357; K T. Potts and C. Hirsch, *J. Org. Chem.*, 1968, **33**, 143.



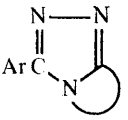
(65)



(66)

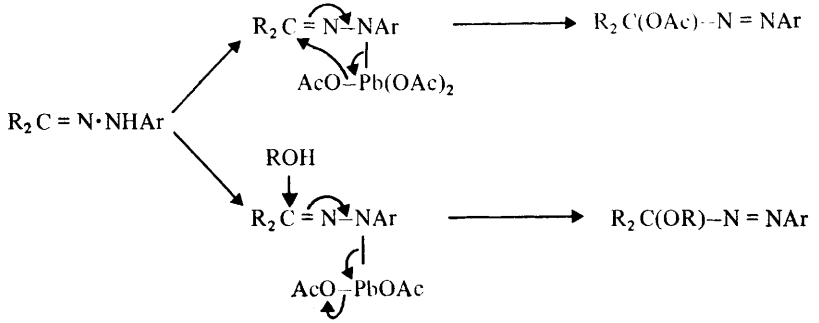


(67)



(68)

Ketone hydrazones are oxidised to azoacetates by an intramolecular displacement mechanism.[100] In alcohol intermolecular displacement of the lead salt yields azoethers.[101]



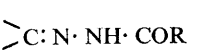
Scheme 23

The azoacetates are useful intermediates in the synthesis of indazoles as on treatment with boron trifluoride they readily lose acetate and cyclise.[4,101] 1-Arylindazoles, 3-substituted 1-arylindazoles, pyridylindazoles, and thienopyrazoles have been synthesised by this method.[100,101] Oxidative cyclisation of ketohydrazones can occur when there is a nucleophilic function in the ketone residue capable of displacing the lead salt from the *N*-lead triacetate intermediate,[102,103] *e.g.* the phenylhydrazone of levulinic acid gives γ-phenylazo-γ-

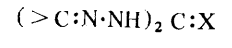
[100] M. J. Harrison, R. O. C. Norman, and W. A. F. Gladstone, *J. Chem. Soc.* (*C*), 1967, 735.
[101] W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc.*, 1965, 3048, 5177; *J. Chem. Soc.* (*C*), 1966, 1527, 1531.
[102] G. B. Gulbelt and J. Warkentin, *Canad. J. Chem.*, 1969, **47**, 3983.
[103] R. Kuhn and W. Munzing, *Ber.*, 1952, **85**, 29.

valerolactone.[102] Amide, alcohol, and carboxyl functions are nucleophilic enough to bring about this cyclisation, while olefinic and ethoxycarbonyl groups are not.[102]

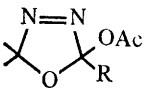
Azoacetates are probable intermediates also in the oxidative cyclisation of *N*-acylhydrazones (69)[104] and diketocarbonohydrazides (70; X = O)[105] to 1,3,4-oxadiazoles (71) and (72; X = O). Diketothiocarbonohydrazides[105] (70; X = S) give thiadiazolines (72; X = S). Appreciable yields of the cyclic materials have been obtained.



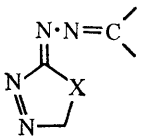
(69)



(70)

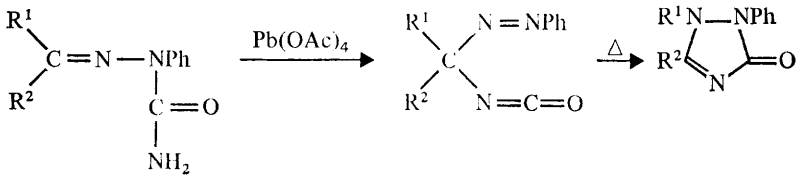


(71)



(72)

A number of semicarbazone derivatives have been oxidised by LTA. Ketone 2-phenylsemicarbazones yield phenylazomethylisocyanates which cyclise with rearrangement to triazolones.[106]

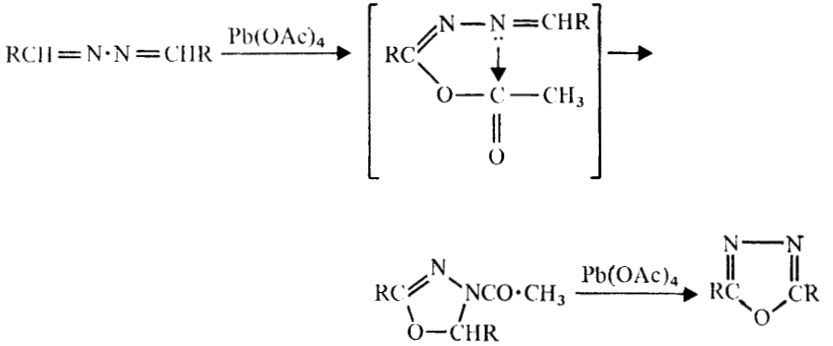


Scheme 24

Ketone 4-monosubstituted semicarbazones yield 1,3,4-oxadiazoles[107] while benzophenone 4,4-diethylsemicarbazones lose nitrogen and yield a carbamate.[108]

[104] R. W. Hoffmann and H. J. Luthardt, *Ber.*, 1968, **101**, 3861.
[105] P. R. West and J. Warkentin, *J. Org. Chem.*, 1968, **33**, 2089.
[106] H. Schildknecht and G. Hatzmann, *Angew. Chem.*, 1968, **7**, 293; 1969, **8**, 456.
[107] A. M. Cameron, P. R. West, and J. Warkentin, *J. Org. Chem.*, 1969, **34**, 32; 30.
[108] D. C. Iffland and T. M. Davies, *J. Amer. Chem. Soc.*, 1963, **85**, 2182.

Aldazines are oxidised to oxadiazolines or their further oxidation products, 2,5-disubstituted 1,3,4-oxadiazoles.[109]

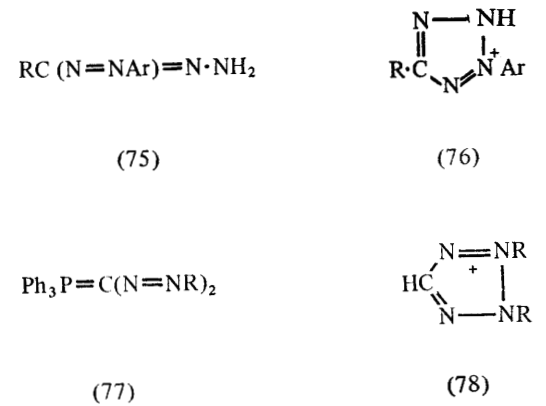


Scheme 25

Aromatic ketazines are unreactive, while aliphatic ketazines (73) yield α,β-unsaturated azoacetates (74).[107]

$RCH_2{\cdot}C(R^1){:}N{\cdot}N{:}CR^2R^3$ (73) $RCH{:}C(R^1){\cdot}N{:}N{\cdot}C(OAc)R^2R^3$ (74)

Formazans (75) are readily oxidised by LTA, as well as by many other oxidants, to tetrazolium salts (76)[110] while the oxidation of triphenylphosphine-



Scheme 26

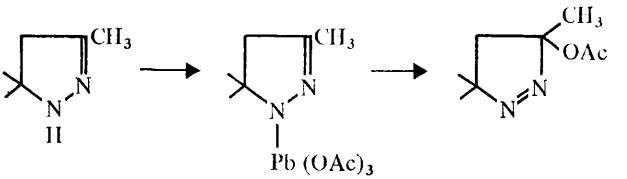
[109] B. T. Gillis and M. P. LaMontagne, *J. Org. Chem.*, 1967, **32**, 3318.
[110] J. N. Ashley, B. M. Davis, A. W. Ninehan, and R. Slack, *J. Chem. Soc.*, 1953, 3881; B. Hirsch, *Annalen*, 1961, **648**, 151; Y. A. Sedov and I. Y. Postovskii, *Zhur. org. Khim.*, 1969, **5**, 781; (*Chem. Abs.*, 1969, **71**, 22074*v*).

bis(arylazo)methylenes (77) with LTA is one of the few ways of synthesising tetrazolium salts with the ring carbon unsubstituted (78).[111]

7 Nitrogen Ring Compounds

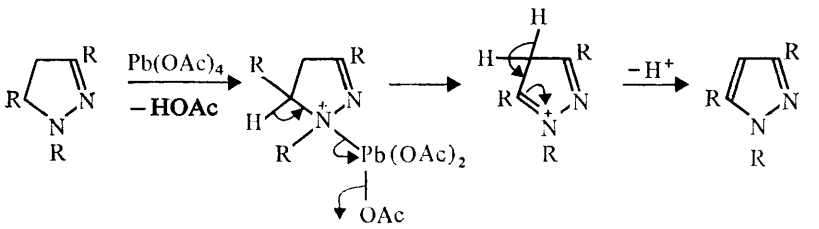
A considerable number of nitrogen containing heterocyclic compounds have been oxidised by LTA. As most of these do not directly involve the nitrogen atom, *e.g.* 2,4-disubstituted pyrroles give their 5,5′-dimers,[112] we shall omit their consideration here.

The oxidation of 2-pyrazolines gives products that vary with the substitution pattern in the pyrazoline ring. 3,5-Disubstituted 2-pyrazolines are oxidised to 3-acetoxy-1-pyrazolines in a reaction similar to that of ketohydrazones.[113,114] The acetoxy derivatives aromatise to pyrazoles on treatment with acid and yield cyclopropylacetates on heating.[115]



Scheme 27

Ethyl-2-pyrazolines,[114] phenylazo-substituted 2-pyrazolines,[115] and *N*,3,5-trisubstituted 2-pyrazolines[116,88] are readily dehydrogenated to pyrazoles. The following mechanism was proposed for the aromatisation of these pyrazolines.[116]



Scheme 28

[111] G. Maerkl, *Z. Naturforsch*, 1962, **17B**, 782.
[112] H. Bauer, *Ber.*, 1968, **101**, 1286.
[113] J. P. Freeman, *J. Amer. Chem. Soc.*, 1964, **29**, 1379; B. R. Davis and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1966, 2006.
[114] R. Kuhn and K. Henkel, *Annalen*, 1941, **549**, 279.
[115] G. F. Duffin and J. D. Kendall, *J. Chem. Soc.* (*C*), 1954, 408.
[116] W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc.* (*C*), 1966, 1536.